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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/246,307	02/08/1999	ALAN P. KOZIKOWSKI	9928-0009-99	6016

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EXAMINER	
GUPTA, ANISH	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/246,307	KOZIKOWSKI ET AL.	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-17,21-28,31,32 and 73-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *23-28,31,32,78-81 and 88-93* is/are allowed.

6)☒ Claim(s) *12-17,21,22,73-77,82-87,94 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-7-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The amendment, filed 11-7-05, is acknowledged. Claims 12 and 75 were amended, claims 82-95 were added. Claims 12-17, 21-28, 31-32, 73-95 are pending in this Application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims remain 12-17, 21-22, 73-77, 82-87 and 94-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for enhancing cognitive function, does not reasonably provide enablement for all other types of neuroprotection in any disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use, the invention commensurate in scope with these claims

Applicants argue that at least 51 patents have issue that utilize the language of effecting neuroprotection. The subject matter of these patent include a wide range of compounds including thienophyrmidiens, nitrate esters, non-estrogen compounds, and calmodulin inhibitors. Given the issuance of these patents with claim language regarding effecting neuroprotection, the claimed invention is enabled.

Applicants further argue that the rejection's utilization of the Martin et al. reference and Mattison et al. reference is misplaced. First, the references do not discuss or even mention the use of bicyclic 2,5-diketopiperazine that are disclosed in the present application. Thus, the reference do not contradict the teachings of the instant application regarding neuroprotection with the compounds claimed. Further, "assuming it is true that it is not understood how cerebral ischemia produces irreversible neural cell death, such a conclusion

is not inconsistent with the discovery that the 2,5-diketopiperazines described in the present invention are useful for effecting neuroprotection." This argument is also pertinent to Mattson et al. and Alzheimer's disease. Applicants have provided considerable evidence based on in vitro and in vivo tests that the compound of the present invention exhibit neuroproteion from various injuries. The examples illustrate mice models for beam walking and spatial learning of mice after being subjected to traumatic injury from incision in the brain from micro-processor-controlled pneumatic impactor. Further, the affidavit by Dr. Faden on October 15, 1999 provides in-vitro evidence using diketopiperazone block neuronal cell deaths after insults specifically implicated in spinal cord injury and stroke. The affidavit also shows an art accepted model for testing neuroprotective effects of the compounds in increased survival of neural cells after traumatic injury. Applicants state that these results are significant since "the various pathological mechanism tested in the experiments described hereinabove. . . .have been proposed as potential mechanism of action for various chronic neurodegenerative disorders (e.g., Alzheimer's disease, ALS, Huntington's disease)." Applicants have also submitted as second declaration which illustrated that representative compounds used in the invention significantly reduced apoptotic cell death caused by beta-amyloid in neuronal cultures. "Beta-amyloid, which is a known causative factor in Alzheimer's disease, has been shown to cause significant cell death when added to neuronal culture in vitro."

Applicants contend that they have references that "refute the position of the United States Patent and Trademark Office that there are no drugs which are effective in neuroprotection." Applicants make reference to 51 patents that claim compound useful in treating neurodegenerative disease including Parkinson's and Alzheimer's disease. Applicants also cite to articles that show the effectiveness of representative compounds in

different animal models subjected to controlled traumatic brain injury (TBI). With respect to Alzheimer's disease, Applicants cite to an article by Dr. Faden, in which the representative compounds disclosed in the present application reduct beta-amyloid induced neural cell death in culture. Further, they exhibit neuroprotection in models of glutamate neutoxicity as well as other models for necrotic cell death. "Since there is strong evidence for the role of glutamate mediated excitotoxicity in experimental TBI and both amyloid β and head injry have been implicated in the pathology of Alzheimer's disease, these data disclose to one of ordinary skill in the at that the diketopiperazine compounds described in the present application are useful for the treatment of Alzheimer's disease." Thus, based upon the disclosure of working examples, the Declarations submitted and the articles presented, one of ordinary skill in the art can only drawn one conclusion, that the amount of experimentation required to make or use the present invention is not undue.

Applicants arguments have been submitted but have not been found persuasive.

First, Applicants contention that " the position of the United States Patent and Trademark Office that there are no drugs which are effective in neuroprotection" is misstated. As indicated in the previous office action, those claims drawn to enhancement of cognitive function were indicated to be allowable. It is further acknowledged that the instant specification is also enabled for neuroprotection form traumatic brain injury (TBI). However, it is still maintained that Applicants have not provided sufficient guidance to treat neuroprotection for the full scope of the claim.

Secondly, Applicants have referenced 51 patents and cited five Articles to support their contention for enablement. With respect to the Patents, Applicants are reminded that each Patent application is prosecuted on its own merits. Further, Applicants pointed out for Martin et al. and Mattison et al., the 51 Patents do not discuss or even mention the use of bicyclic 2,5-diketopiperazine. Thus, while the citations of the 51 Patents are acknowledged, they do little to offer support for enablement with respect to the instant claims.

With respect to the articles submitted, it is noted that all of the articles cited were published after 2003. Applicants filing date for the instant application is 1999, with a claim of benefit to 1998. The MPEP states that "[t]he state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. Chiron Corp. v.Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004). . . .Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976)." See MPEP 2164.05(a).

Assuming arguendo, that the references are applicable, they do not provide guidance as to neuroprotection with respect to Alzheimer's. All of the references cited provide insight into the assessment of representative compounds with respect to traumatic brain injuries and not Alzheimer's or necrotic cell death. Even the article cited by Applicant in Journal of Alzheimer's Disease speaks of traumatic brain injury. While the reference may state that one compound, 35b, was effective in as a neuroprotection glutamate or amyloid-beta neurotoxicity, the reference does not supply any evidence, beyond theoretical evidence, that the compounds provide neuroprotection in Alzheimer diseased patients. The reference does not provide data, in vitro or in vivo, that illustrate the effects of the compounds on

Alzheimer diseased brain cells. In fact that the reference states that the in vitro studies "**potentially** [provide support for] chronic neurodegenerative disorders." This potential assessment if far from the conclusion, that the amount of experimentation required to make or use the present invention is not undue, as Applicants have asserted.

As stated in the previous office action, "At the present time there is no effective pharmacological therapy available which can either cure Alzheimer's disease or stop the progression." Furthermore, the hallmark of the Alzheimer's disease is amyloid deposition. The specification does not reasonably provide any guidance that the compounds can effectively provide "neuroprotection" against amyloid deposition in either decreasing the progression or stopping them all together. Hsiao et al. disclose that amyloid deposition, even where therapy results in cognition enhancement, does not result in amelioration of amyloid deposition (see page 102). Thus, one of ordinary skill with the knowledge about the effects of a single compound in glutamate or amyloid beta neurotoxicity would be burdened with undue experimentation. The artisan would have to determine the effects using Alzheimer diseased brain cells and then determine the effects of neuroprotection on animal models and finally humans. This would be undue experimentation. Finally, it should be noted that one of the references cited by Applicants state "[t]raditionally, neuroprotection treatment approaches have focused on single receptors or injury factors, and have been primarily aimed at reducing neurotic cell death. Because necrosis is an early event, and it is often not possible to treat patients until many hours after acute injures, such strategies are not likely to be effective. Indeed, virtually all neurprotective treatment trials in stroke or traumatic brain injury have failed." (see Yakovlev et al. page 12). This statement illustrates that while initial experimentation some insight into the effectiveness of a drug, it is not a conclusive assessment into its in-vivo effectiveness. Applicants specification and the

Declarations, simply fail to provide sufficient guidance, at the time the Application was filed, to fully enable the claimed invention.

Rejection is maintained.

3. Claims 23-28, 31-32, and 78-81, 88-93 are allowed.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can normally be reached on (571) 272-0974. The fax phone number of this group is (571)-273-8300.